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- (71) Applicant (for all designated States except US): **AXYS
PHARMACEUTICALS, INC.** [US/US]; 180 Kimball
Way, So. San Francisco, CA 94080 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **GRAUPE, Michael**
[AT/US]; 1131 Banyan Way, Pacifica, CA 94044 (US).
LAU, Agnes, J. [MY/US]; 595 John Muir Drive, San
Francisco, CA 94132 (US). **LINK, John, O.** [US/US]; 12
Prospect Avenue, San Francisco, CA 94110 (US). **LIU,
Yang** [CN/US]; 643 Catamaran Street, Foster City, CA
94404 (US). **MOSSMAN, Craig, J.** [US/US]; 282 War-
wick Drive, Campbell, CA 98005 (US). **PATTERSON,
John, W.** [US/US]; 1619 Montalto Drive, Mountain View,
CA 94040 (US). **ZIPFEL, Shella, M.** [US/US]; 112 E.
Middlefield Road, Unit B, Mountain View, CA 94043
(US).
- (74) Agents: **BANSAL, Rekha et al.**; Celera, an Applera Busi-
ness Corporation, 180 Kimball Way, So. San Francisco,
CA 94080 (US).
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- For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CYANOMETHYL DERIVATIVES AS CYSTEINE PROTEASE INHIBITORS

(57) Abstract: The present invention is directed to cyanomethyl derivatives that are inhibitors of cysteine protease, in particular, cathepsins B, K, L, F, and S and are therefore useful in treating diseases mediated by these proteases. The present invention is directed to pharmaceutical compositions comprising these compounds and processes for preparing them.

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INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 03/37979

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K5/062 A61K38/05 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/24460 A (NOVARTIS ERFIND VERWALT GMBH ;ALTMANN EVA (CH); LATTMANN RENE (CH)) 20 May 1999 (1999-05-20) page 1, lines 1-3; page 6, lines 4-9; page 31, compound 13; page 43, compound 49; page 58, compound 110; page 61, compound 130; claims 1,2 ---	1-37
X	WO 00/55126 A (BRYANT CLIFFORD M ;VENKATRAMAN SHANKAR (US); AXYS PHARM INC (US);) 21 September 2000 (2000-09-21) page 26, line 27 -page 27, line 12; claim 1 --- -/--	1-37

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Grammenoudi, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/37979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/58886 A (NOVARTIS ERFINDE VERWALT GMBH ;NOVARTIS AG (CH); MISSBACH MARTIN (C) 16 August 2001 (2001-08-16) page 1, line 1-4 page 1, line 17 -page 2, line 8; claim 1 ---	1-37
X	WO 00/49008 A (EDWARDS PHILIP NEIL ;LARGE MICHAEL STEWART (GB); OLDFIELD JOHN (GB) 24 August 2000 (2000-08-24) page 1, line 1-6; claim 1 ---	1-37
X	WO 01/19816 A (BOEHRINGER INGELHEIM PHARMA ;EMMANUEL MICHEL J (US); FRYE LEAH L () 22 March 2001 (2001-03-22) page 1, line 11-15 page 6, line 25 -page 11, line 8; claim 1 ---	1-37
X	WO 00/51998 A (BOEHRINGER INGELHEIM PHARMA) 8 September 2000 (2000-09-08) page 1, line 9-13 page 78, line 19 -page 81, line 9; claims 21,31 -----	1-37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/37979

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 34-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9924460 A	20-05-1999	AU 751669 B2	22-08-2002
		AU 1487399 A	31-05-1999
		BR 9813197 A	29-08-2000
		CA 2306313 A1	20-05-1999
		CN 1278244 T	27-12-2000
		WO 9924460 A2	20-05-1999
		EP 1028942 A2	23-08-2000
		HU 0004400 A2	29-04-2002
		ID 24931 A	31-08-2000
		JP 2001522862 T	20-11-2001
		NO 20002320 A	04-07-2000
		NZ 503889 A	26-07-2002
		PL 340819 A1	26-02-2001
		SK 6572000 A3	09-10-2000
		TR 200001189 T2	21-09-2000
		US 2004029814 A1	12-02-2004
		US 6353017 B1	05-03-2002
		ZA 9810073 A	05-05-1999
		TW 527362 B	11-04-2003
WO 0055126 A	21-09-2000	AT 259782 T	15-03-2004
		AU 3746100 A	04-10-2000
		AU 769736 B2	05-02-2004
		AU 3748600 A	04-10-2000
		BG 106003 A	28-06-2002
		BG 106013 A	31-05-2002
		BR 0009042 A	26-12-2001
		BR 0009043 A	08-01-2002
		CA 2368122 A1	21-09-2000
		CA 2368148 A1	21-09-2000
		CN 1362947 T	07-08-2002
		CN 1364155 T	14-08-2002
		CZ 20013217 A3	17-04-2002
		CZ 20013248 A3	17-04-2002
		DE 60008369 D1	25-03-2004
		EE 200100485 A	17-02-2003
		EE 200100487 A	17-02-2003
		EP 1178958 A2	13-02-2002
		EP 1161415 A2	12-12-2001
		HR 20010737 A1	31-10-2002
		HR 20010738 A1	31-12-2002
		HU 0200347 A2	29-06-2002
		HU 0200503 A2	29-06-2002
		JP 2002539191 T	19-11-2002
		JP 2002539192 T	19-11-2002
		NO 20014484 A	26-10-2001
		NO 20014485 A	05-11-2001
		NZ 514234 A	27-02-2004
		PL 350453 A1	16-12-2002
		PL 350456 A1	16-12-2002
		SK 12882001 A3	04-04-2002
		SK 12892001 A3	04-06-2002
		TR 200103337 T2	21-03-2002
		TR 200103390 T2	21-05-2002
		TR 200201874 T2	21-10-2002
		WO 0055125 A2	21-09-2000
		WO 0055126 A2	21-09-2000
		US 2002086996 A1	04-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0055126	A		US	2003096796 A1	22-05-2003
			US	2003119788 A1	26-06-2003
			US	6455502 B1	24-09-2002
			US	6476026 B1	05-11-2002
			ZA	200107494 A	11-09-2002
			ZA	200107495 A	11-09-2002
WO 0158886	A	16-08-2001	AU	764334 B2	14-08-2003
			AU	4642601 A	20-08-2001
			BR	0108118 A	25-02-2003
			CA	2396158 A1	16-08-2001
			CN	1398260 T	19-02-2003
			CZ	20022721 A3	13-11-2002
			WO	0158886 A1	16-08-2001
			EP	1254124 A1	06-11-2002
			HU	0300148 A2	28-05-2003
			JP	2003522764 T	29-07-2003
			NO	20023780 A	09-08-2002
			NZ	519940 A	27-02-2004
			SK	11462002 A3	09-01-2003
			TR	200201752 T2	21-10-2002
			US	2003203919 A1	30-10-2003
			US	2001016207 A1	23-08-2001
			ZA	200206218 A	05-08-2003
WO 0049008	A	24-08-2000	AU	2560000 A	04-09-2000
			EP	1155011 A1	21-11-2001
			WO	0049008 A1	24-08-2000
			JP	2002537294 T	05-11-2002
WO 0119816	A	22-03-2001	AT	244235 T	15-07-2003
			AU	7081800 A	17-04-2001
			BG	106483 A	31-10-2002
			CA	2385130 A1	22-03-2001
			CN	1384830 T	11-12-2002
			CZ	20020844 A3	12-06-2002
			DE	60003702 D1	07-08-2003
			DE	60003702 T2	22-04-2004
			DK	1218372 T3	20-10-2003
			EE	200200132 A	15-12-2003
			EP	1218372 A1	03-07-2002
			ES	2199856 T3	01-03-2004
			HU	0302380 A2	01-03-2004
			JP	2003529546 T	07-10-2003
			NO	20021207 A	12-03-2002
			PT	1218372 T	28-11-2003
			SI	1218372 T1	31-12-2003
			SK	4902002 A3	10-09-2002
			US	2002058809 A1	16-05-2002
			WO	0119816 A1	22-03-2001
			US	2003225271 A1	04-12-2003
			US	2003225270 A1	04-12-2003
			US	6420364 B1	16-07-2002
WO 0051998	A	08-09-2000	CA	2360740 A1	08-09-2000
			EP	1159273 A1	05-12-2001
			JP	2002538151 A	12-11-2002
			US	6608057 B2	19-08-2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/37979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0051998	A	US 2002091259 A1	11-07-2002
		WO 0051998 A1	08-09-2000
		US 2003158406 A1	21-08-2003
		US 6395897 B1	28-05-2002
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